PATENT COOPERATION TREATY

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INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

REC'D 21 MAY 2004

WIPO PCT

Applicant's or agent's file reference SAC/P33031WO	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/GB 03/01550	International filing date *(day/month/year)* 10.04.2003	Priority date *(day/month/year)* 10.04.2002
International Patent Classification (IPC) or both national classification and IPC C07D401/12		
Applicant GLAXO GROUP LIMITED et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 6 sheets, including this cover sheet.

   ☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the opinion
   - II ☐ Priority
   - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
23.10.2003	18.05.2004
Name and mailing address of the international preliminary examining authority: European Patent Office - Gitschiner Str. 103 D-10958 Berlin Tel. +49 30 25901 - 0 Fax: +49 30 25901 - 840	Authorized Officer Hass, C Telephone No. +49 30 25901-340

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/GB 03/01550

I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:

Description, Pages

1-56 as originally filed

Claims, Numbers

1-18 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

   These elements were available or furnished to this Authority in the following language: , which is:

   ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).

   ☐ the language of publication of the international application (under Rule 48.3(b)).

   ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

   ☐ contained in the international application in written form.

   ☐ filed together with the international application in computer readable form.

   ☐ furnished subsequently to this Authority in written form.

   ☐ furnished subsequently to this Authority in computer readable form.

   ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

   ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

   ☐ the description, pages:

   ☐ the claims, Nos.:

   ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)).

   (Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

   ☐ the entire international application,

   ☒ claims Nos. 17 (with regard to industrial applicability)

   because:

   ☒ the said international application, or the said claims Nos. 17 relate to the following subject matter which does not require an international preliminary examination (specify):

   see separate sheet

   ☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

   ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

   ☐ no international search report has been established for the said claims Nos.

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

   ☐ the written form has not been furnished or does not comply with the Standard.

   ☐ the computer readable form has not been furnished or does not comply with the Standard.

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-18
	No:	Claims	
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-18
Industrial applicability (IA)	Yes:	Claims	1-16, 18
	No:	Claims	

2. Citations and explanations

   see separate sheet

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

Claim 17 relates to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of this claim (Article 34(4)(a)(i) PCT).

Re Item V

Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Cited documents

D1: WO 01 60805 A (SMITH STEPHEN ALLAN; IFE ROBERT JOHN (GB); PINTO IVAN LEO (GB); HI) 23 August 2001 (2001-08-23)

D2: WO 00 66567 A (FENWICK ASHLEY EDWARD; SMITH STEPHEN ALLAN (GB); IFE ROBERT JOHN () 9 November 2000 (2000-11-09) cited in the application

D3: WO 00 10980 A (SMITH STEPHEN ALLAN; LEACH COLIN ANDREW (GB); SMITHKLINE BEECHAM P) 2 March 2000 (2000-03-02) cited in the application

D4: WO 99 24420 A (SMITH STEPHEN ALLAN; IFE ROBERT JOHN (GB); PINTO IVAN LEO (GB); HI) 20 May 1999 (1999-05-20) cited in the application

2. Novelty

2.1 The subject-matter of claim 1 differs from the disclosure of D1 only in that the R^4-corresponding moiety in D1 is a heterocyclyl group, whereas the present R^4 group is benzimidazole or heteroaryl. In the broadest sense, "heterocyclyl" comprises "heteroaryl", however, the respective concrete examples in D1 (examples 27 and 67) refer to piperidine only (which is not aromatic), so that R^4 may be considered as differentiating feature towards D1. Consequently, the subject-matter of claim 1 and of

claims 2-18 may be considered novel with regard to D1.

2.2 D2 to D4 do not disclose novelty-destroying subject-matter either.

3. Inventive step

3.1 According to the description, the problem underlying the present application is to provide further pyrimidinone and pyridinone derivatives which are useful in the treatment of atherosclerosis.

3.2 With the compounds of D1-D4, the problem to provide pyrimidinone derivatives useful in the treatment of atherosclerosis has already been solved.

3.3 D1 is considered to represent the closest prior art. The compounds disclosed in D1, claim 1, come structurally very close to the compounds of present claim 1 (the expression "5- or 6-membered heteroaryl" used in present claim 1 in connection with R^4 could be considered to be generically comprised by the term "5- to 7-membered heterocyclyl ring comprising N and optionally O or S", used in claim 1 of D1 in connection with the corresponding R^3). Moreover, the D1 compounds have the same activity profile as the present compounds, and, furthermore, the screening for Lp-PLA_2 inhibition resulted in absolutely comparable IC_{50} values, the best of which are <0.1 nM in D1 (page 41) as well as in the present application (page 56). Therefore the present compounds bear no structural or pharmacological feature which makes them significantly different from the D1 compounds; the compounds presently claimed must be considered as to represent an obvious result from the prior art, especially from D1. Inventive step is thus to be denied for present claim 1 as well as for dependent claims 2 to 13 and for pharmaceutical claims 14 to 17. Inventive step for process claim 18 could only be given if the process results in compounds which could be considered inventive; it is noted that the presently claimed process is analogous to the process claimed in claim 20, part (a) of D2. Therefore inventive step must also be denied for process claim 18.

4. Industrial applicability

4.1 The subject-matter of claims 1-16 and 18 is industrially applicable.

4.2 For the assessment of the present claim 17 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

5. Miscellaneous

5.1 Claim 13 does not comply with Rule 6(2)(a) PCT since its relies on references to the description (i.e. the examples).

5.2 There are some mistakes in connection with the citations on page 2 of the description:
"WO 96/12963" does not deal with inhibitors of the enzyme Lp-PLA_2.
"WO 97/217675" should read "WO 97/21676";
"WO 97/217676" shouid read "WO 97/21676";
"WO 96/41098" should read "WO 97/41098".
"PCT/EP01/11562" has now been published as "WO 02/30911", and
"PCT/EP01/11610" has now been published as "WO 02/30904".